

The Prevention of Ovarian Hyperstimulation Syndrome

This clinical practice guideline has been prepared by the Reproductive Endocrinology Infertility Committee and approved by Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objective: To review the clinical aspects of ovarian hyperstimulation syndrome and provide recommendations on its prevention.

Options: Preventative measures, early recognition, and prompt systematic supportive care will help avoid poor outcomes.

Outcomes: Establish guidelines to assist in the prevention of ovarian hyperstimulation syndrome, early recognition of the condition when it occurs, and provision of appropriate supportive measures in the correct setting.

Evidence: Published literature was retrieved through searches of Medline, Embase, and the Cochrane Library from 2011 to 2013 using appropriate controlled vocabulary ([OHSS] ovarian hyperstimulation syndrome and: agonist IVF, antagonist IVF, metformin, HCG, gonadotropin, coasting, freeze all, agonist trigger, progesterone) and key words (ovarian hyperstimulation syndrome, ovarian stimulation, gonadotropin, human chorionic gonadotropin, prevention). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies published in English. There were no date restrictions. Searches were updated on a regular basis and incorporated in the guideline to February 2013.

Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Values: The quality of evidence in this document was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

Summary Statements

1. The particular follicle-stimulating hormone formulation used for ovarian stimulation does not affect the incidence of ovarian hyperstimulation syndrome. (I)
2. Coasting may reduce the incidence of severe ovarian hyperstimulation syndrome. (III)

Key Words: Ovarian hyperstimulation syndrome, ovarian stimulation, gonadotropin, human chorionic gonadotropin, prevention

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Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.⁶⁵

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.⁶⁵

- Coasting for longer than 3 days reduces in vitro fertilization pregnancy rates. (II-2)
- The use of either luteinizing hormone or human chorionic gonadotropin for final oocyte maturation does not influence the incidence of ovarian hyperstimulation syndrome. (I)
- There is no clear published evidence that lowering the human chorionic gonadotropin dose will result in a decrease in the rate of ovarian hyperstimulation syndrome. (III)
- Cabergoline starting from the day of human chorionic gonadotropin reduces the incidence of ovarian hyperstimulation syndrome in patients at higher risk and does not appear to lower in vitro fertilization pregnancy rates. (II-2)
- Avoiding pregnancy by freezing all embryos will prevent severe prolonged ovarian hyperstimulation syndrome in patients at high risk. (II-2)
- Pregnancy rates are not affected when using gonadotropin-releasing hormone (GnRH) agonists in GnRH antagonist protocols for final egg maturation when embryos are frozen by vitrification for later transfer. (II-2)

Recommendations

- The addition of metformin should be considered in patients with polycystic ovarian syndrome who are undergoing in vitro fertilization because it may reduce the incidence of ovarian hyperstimulation syndrome. (I-A)
- Gonadotropin dosing should be carefully individualized, taking into account the patient's age, body mass, antral follicle count, and previous response to gonadotropins. (II-3B)
- Cycle cancellation before administration of human chorionic gonadotropin is an effective strategy for the prevention of ovarian hyperstimulation syndrome, but the emotional and financial burden it imposes on patients should be considered before the cycle is cancelled. (III-C)
- Gonadotropin-releasing hormone (GnRH) antagonist stimulation protocols are recommended in patients at high risk for ovarian hyperstimulation syndrome (OHSS). The risk of severe OHSS in patients on GnRH antagonist protocols who have a very robust ovarian stimulation response can be reduced by using a GnRH agonist as a substitute for human chorionic gonadotropin to trigger final oocyte maturation. (I-B)
- A gonadotropin-releasing hormone (GnRH) antagonist protocol with a GnRH agonist trigger for final oocyte maturation is recommended for donor oocyte and fertility preservation cycles. (III-C)
- Albumin or other plasma expanders at the time of egg retrieval are not recommended for the prevention of ovarian hyperstimulation syndrome. (I-E)
- Elective single embryo transfer is recommended in patients at high risk for ovarian hyperstimulation syndrome. (III-C)

ABBREVIATIONS

ART	assisted reproductive technology
CI	confidence interval
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
hCG	human chorionic gonadotropin
HES	hydroxyethyl starch
IVF	in vitro fertilization
LH	luteinizing hormone
LPS	luteal phase support
OHSS	ovarian hyperstimulation syndrome
OR	odds ratio
PCOS	polycystic ovary syndrome
RCT	randomized control study
SC	subcutaneously
VEGF	vascular endothelial growth factor

8. Progesterone, rather than human chorionic gonadotropin, should be used for luteal phase support. (I-A)
9. Outpatient culdocentesis should be considered for the prevention of disease progression in severe ovarian hyperstimulation syndrome. (II-2B)

INTRODUCTION

OHSS is a iatrogenic complication of exogenous gonadotropin therapy used to mature multiple follicles for assisted reproductive treatments. The syndrome is only rarely observed with clomiphene citrate treatment but has been reported even after spontaneous ovulation.¹ Published guidelines already exist on the management of patients suffering from severe OHSS.² The goal of this guideline is to provide a practical, evidence-based framework for the prevention of OHSS.

After gonadotropin stimulation for IVF, the reported incidence of moderate OHSS is 3% to 6%, and for severe OHSS it is 0.1% to 2%.^{3,4} The mild form, which has little clinical consequence, occurs in about 20% to 33% of IVF cycles^{3,5} and is of little clinical concern. However, fatalities have been reported in the most severe cases.⁶ Except during rare events, OHSS occurs only after ovulation (i.e. after exposure to an endogenous LH surge, to exogenous LH or hCG, or to endogenous hCG of pregnancy).⁷ Early OHSS symptoms may begin as soon as 24 hours after hCG administration, but become most severe 7 to 10 days after hCG; severe OHSS is usually associated with the rise of endogenous hCG from an early pregnancy⁸ (see Table 2).

Physicians prescribing ovarian stimulation need to identify patients at increased risk for OHSS in order to apply preventive and active management strategies to minimize morbidity from this complication of fertility treatment.

Pathophysiology of OHSS

OHSS is a systemic disease thought to result from vasoactive peptides released from the granulosa cells in hyperstimulated ovaries.⁷ The fundamental physiological change in severe OHSS is an increase in vascular permeability, resulting in a fluid shift from the intravascular spaces to third-space compartments such as the peritoneal and thoracic cavities, often resulting in hemoconcentration.^{9,10} The most important mediator in this process is thought to be VEGF.¹¹ Supporting evidence comes from studies showing that serum VEGF levels correlate with OHSS severity. Additionally, hCG has been shown to increase VEGF expression in human granulosa cells, which in turn raises serum VEGF concentration.^{12,13} A new body of clinical data demonstrates how the administration of dopamine agonist drugs decreases VEGF activity, which in

Table 2. Classification of OHSS

Grade	Symptoms
Mild OHSS	Abdominal bloating Mild abdominal pain Ovarian size usually < 8 cm
Moderate OHSS	Moderate abdominal pain Nausea with/without vomiting Ultrasound evidence of ascites Ovarian size usually 8–12 cm
Severe OHSS	Clinical ascites (occasionally pleural effusion) Oliguria Hemoconcentration hematocrit (> 45%) Hypoproteinemia Ovarian size usually > 12 cm
Critical OHSS	Tense ascites or large pleural effusion Hematocrit (> 55%) White cell count > 25 000/L Oligo/anuria Thromboembolism Acute respiratory distress syndrome

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turn decreases the clinical burden of OHSS.¹⁴ Numerous other mediators have been implicated in the disease process such as angiotensin II, insulin-like growth factor 1 and interleukin-6.²

Risk Factors

Several factors have been demonstrated to independently increase the risk of developing OHSS. These include

- age < 30 years,¹⁵
- polycystic ovaries (i.e., > 24 antral follicles present on baseline ultrasound examination),^{16,17}
- high serum estradiol at hCG trigger or rapidly rising serum estradiol,¹⁵
- previous episodes of OHSS,¹⁸
- large number of small follicles (8 to 12 mm) seen on ultrasound during ovarian stimulation,¹⁷
- use of hCG, as opposed to progesterone, for luteal phase support after IVF,¹⁸
- large number of oocytes retrieved (> 20),¹⁹ and
- high anti-müllerian hormone (> 3.36 ng/mL).²⁰

PREVENTION

Physicians providing ART treatment must balance the competing interests of trying to sufficiently stimulate the

ovary to optimize the chance of achieving a pregnancy and minimizing the risk of severe OHSS. To achieve both of these goals both primary and secondary preventative measures have been shown to be useful.¹

Primary prevention involves identifying risk factors for OHSS and choosing an appropriate ovarian stimulation regimen. Secondary prevention involves recognizing patients who are over-responsive to gonadotropins and intervening to reduce the risk of OHSS while still trying to salvage the treatment cycle.

A meta-analysis of 5 RCTs showed a significant reduction in the incidence of OHSS with the use of metformin in women with PCOS undergoing IVF (12/216 vs. 44/210; OR 0.21, 95% CI 0.11 to 0.41, $P < 0.01$).²¹ These findings were later corroborated in a Cochrane review from the same group.²² Interestingly, a recent RCT showed that women with polycystic ovarian morphology that does not meet the criteria for PCOS do not incur the same protective benefit from metformin of reduced OHSS.²³

Metformin should ideally be started 8 weeks before planned gonadotropin stimulation to be effective in OHSS prevention. To minimize gastrointestinal side effects we recommend starting Metformin at a low dose of 500 mg HS and slowly increasing the dose until the effective dose of 500 mg \times 3 (1500 mg) daily is reached. Metformin should continue until egg retrieval.

Two separate meta-analyses of RCTs comparing recombinant FSH and urinary FSH showed no difference in the incidence of OHSS.^{24,25}

There is no linear positive correlation between gonadotropin dose and the incidence of severe OHSS. On the contrary, patients developing OHSS tend to be those who respond robustly to gonadotropins and are often prescribed lower than average doses of these drugs than other women undergoing IVF. Young, thin women, especially those with polycystic ovaries on ultrasound (i.e., > 12 antral follicles seen on each ovary) are at higher risk for OHSS and should receive a lower starting dose of gonadotropin than would be given to other women.²⁶ Careful monitoring of these patients during stimulation is prudent to allow for a decrease in the dose of gonadotropins if a very robust response is detected early in the treatment cycle.¹⁸

Summary Statement

1. The particular follicle-stimulating hormone formulation used for ovarian stimulation does not affect the incidence of ovarian hyperstimulation syndrome. (I)

Recommendations

1. The addition of metformin should be considered in patients with polycystic ovarian syndrome who are undergoing in vitro fertilization because it may reduce the incidence of ovarian hyperstimulation syndrome. (I-A)
2. Gonadotropin dosing should be carefully individualized, taking into account the patient's age, body mass, antral follicle count, and previous response to gonadotropins. (II-3B)

Coasting

Coasting involves withholding gonadotropins while maintaining pituitary suppression with a gonadotropin-releasing hormone agonist or antagonist. Administering hCG to trigger oocyte maturation once estrogen levels plateau or drop is thought to reduce the risk for OHSS. Larger follicles have a lower requirement for FSH than smaller follicles. Once follicles are > 12 mm in diameter, stopping all gonadotropins still allows for larger follicles to continue their growth and maturation, while smaller follicles undergo atresia, which may result in reduced production of vasoactive peptides such as VEGF.²⁷ It has been shown that coasting on a GnRH agonist for up to 3 days does not adversely affect pregnancy rates.²⁸ The same criteria for coasting can be applied to GnRH antagonist cycles as to GnRH agonist cycles with similar IVF outcomes.²⁹

In a systematic review of 12 retrospective studies examining the benefit of coasting, the coasted patients had a 2.5% incidence of hospitalization for OHSS, which is lower than expected for patients at high risk for OHSS.³⁰ Previous studies have shown a significant drop in pregnancy rate with longer than 3 to 4 days of coasting.^{28,31} Therefore, cycle cancellation should be considered if estradiol levels do not start to fall by the fourth day of coasting.

A meta-analysis of 3 RCTs comparing recombinant LH with urinary hCG for triggering final oocyte maturation and 11 RCTs comparing recombinant hCG with urinary LH did not show any difference in the risk of OHSS.³²

Summary Statements

2. Coasting may reduce the incidence of severe ovarian hyperstimulation syndrome. (III)
3. Coasting for longer than 3 days reduces in vitro fertilization pregnancy rates. (II-2)
4. The use of either luteinizing hormone or human chorionic gonadotropin for final oocyte maturation does not influence the incidence of ovarian hyperstimulation syndrome. (I)

The degree of hCG exposure has been associated with the risk of OHSS.¹⁸ It is recognized that hCG has no direct effect on the vascular system³³; however, vasoactive substances such as VEGF are released in the ovary in response to hCG administration and are most likely responsible for inducing vascular hyperpermeability and third-spacing in high-risk women.³⁴ A retrospective series of 94 IVF cycles showed that when hCG doses were lowered, both pregnancy rates and the rate of severe OHSS remained unchanged.³⁵ However, a lower incidence of severe OHSS has been observed with the use of lower doses of hCG for final oocyte maturation in an at-risk population. Because serum levels of hCG are dependent on body mass,^{36,37} one Canadian fertility centre uses hCG 5000 IU SC to trigger final egg maturation in patients at risk for OHSS who have a BMI < 28 kg/m², despite the lack of published data. Women with a BMI ≥ 28 kg/m² are all given hCG 10 000 IU SC for final egg maturation because yields of mature eggs have been observed to be lower with a dose reduction in this population.³⁶

Summary Statement

5. There is no clear published evidence that lowering human chorionic gonadotropin dose will result in a decrease in the rate of ovarian hyperstimulation syndrome. (III)

Cabergoline

VEGF produced by granulosa cells of developing follicles is thought to be a key mediator in both hCG-dependent ovarian angiogenesis and the pathophysiology of OHSS.³⁸ Recently, the dopamine agonist cabergoline has been introduced as a secondary prevention strategy in women deemed to be at high risk for OHSS because of a very robust gonadotropin response at the end of a controlled ovarian stimulation cycle. Dopamine agonists show similar effects to anti-angiogenic drugs on vascular permeability, and except for occasional nausea, they appear not to have undesirable side effects.^{33,39} Evidence from animal models shows that cabergoline blocks VEGF-mediated increase in vascular permeability without affecting angiogenesis.³³ Cabergoline's postulated mechanism of action is partial inhibition of the phosphorylation of its associated receptor, the VEGF receptor 2.⁴⁰

A recent Cochrane review included 2 RCTs addressing cabergoline and OHSS. In the RCT conducted by Alvarez et al. on oocyte donors at risk for OHSS (20 to 30 follicles at > 12 mm and > 20 eggs retrieved), in which the treatment group received oral cabergoline 0.5 mg daily for 8 days starting on the day of hCG and the control group received a placebo, the incidence of moderate OHSS was significantly reduced in the cabergoline group (20% vs.

43.8%, $P = 0.04$).¹⁴ The same first author also showed that pregnancy rates are not compromised in patients given cabergoline.⁴¹ The second RCT by Carriza et al. randomized women who were undergoing IVF and at high risk for OHSS (estradiol ≥ 14 700 pmol/L on day of hCG trigger) into two groups: the study group received 20 grams of prophylactic intravenous albumin and 0.5 mg of Cabergoline orally once daily for 3 weeks commencing the day after oocyte retrieval and the control group received only albumin.⁴² The risk of early OHSS (occurring within the first 9 days after hCG trigger) decreased significantly ($P < 0.001$) in the cabergoline group; none of the patients who had taken cabergoline progressed to early OHSS, but 15.0% of the control group did. The risk of late OHSS did not decrease. In both of the RCTs examined, the use of cabergoline did not affect the pregnancy outcome (clinical pregnancy rate or miscarriage rate), nor was it associated with an increased risk of adverse events.⁴³

Two published abstracts have demonstrated the safety and efficacy of using cabergoline at even smaller doses: 0.5 mg twice weekly for 6 doses⁴⁴ and 0.5 mg twice weekly for 3 doses.⁴⁵ Clinicians at one Canadian fertility centre use a dose of cabergoline 0.5 mg every 3 days to a total of 4 doses starting on the day of oocyte maturation trigger and a significant reduction in the incidence of severe OHSS has been anecdotally observed since the introduction of cabergoline into the prevention strategies for OHSS.

Although still somewhat preliminary, current data suggest that cabergoline is associated with a reduction in moderate OHSS in patients at high risk and has no adverse effect on the pregnancy rate.

Summary Statement

6. Cabergoline starting from the day of human chorionic gonadotropin reduces the incidence of ovarian hyperstimulation syndrome in patients at higher risk and does not appear to lower in vitro fertilization pregnancy rates. (II-2)

Cycle Cancellation

OHSS will not develop in the absence of exposure to exogenous hCG or LH or to an endogenous LH surge as long as a pregnancy does not develop. Therefore, withholding hCG in cycles at risk for OHSS and cancelling the cycle is the most effective method of preventing OHSS. This prevention strategy is especially important in agonist cycles in which the option to substitute an agonist trigger for hCG does not exist. However, because the emotional and financial costs of cancellation are significant, other prevention strategies should be exhausted before cycle cancellation is considered.

Recommendation

3. Cycle cancellation before the administration of human chorionic gonadotropin is an effective strategy for the prevention of ovarian hyperstimulation syndrome, but the emotional and financial burden it imposes on patients should be considered before the cycle is cancelled. (III-C)

PROTOCOLS

Assisted reproductive technologies, especially IVF protocols, generally use GnRH agonists or antagonists to prevent an endogenous LH surge from occurring before follicular maturation. A Cochrane review of 29 RCTs showed a significantly lower incidence of OHSS in GnRH antagonist cycles than in GnRH agonist cycles (OR 0.43; 95% CI 0.33 to 0.57). Differences in rates of pregnancy or live births were not observed between the two protocols.⁴⁶

One important benefit of using GnRH antagonist protocols in patients at risk for OHSS (e.g., PCOS patients) is that final oocyte maturation can be achieved using a GnRH agonist instead of hCG. In a GnRH antagonist protocol, a GnRH agonist trigger will displace the GnRH antagonist from the GnRH receptor to induce a controlled surge of endogenous LH and FSH. This GnRH agonist-induced LH has a shorter half-life than exogenous hCG, resulting in a less sustained luteotrophic stimulation and hence a lower risk for OHSS.⁴⁷ GnRH agonist triggering may prevent early OHSS. OHSS is rarely encountered in IVF egg donors when GnRH agonist is used to trigger final oocyte maturation.⁴⁷

An important potential concern when using a GnRH agonist trigger during GnRH antagonist IVF cycles is the possible risk of having an inadequate luteal phase. A single dose of GnRH agonist induces an endogenous LH surge that has a much shorter half-life than hCG, resulting in compromised corpus luteum formation⁴⁸ and a shorter duration of the luteal phase.⁴⁹ Initial reports showed poor clinical outcomes with a higher incidence of early pregnancy loss and compromised pregnancy rates when a GnRH agonist was used for final oocyte maturation.^{50,51} Subsequent transfer of frozen-thawed embryos from patients with a GnRH agonist trigger showed improved pregnancy rates and spontaneous abortion rates similar to those in patients using an hCG trigger. These data suggest that the etiology of the observed lower success rates in fresh cycles triggered with GnRH agonist is due to endometrial problems in the luteal phase rather than to an effect on embryo quality.⁵²

More recent studies have addressed these concerns by employing a more comprehensive LPS protocol after final oocyte maturation with GnRH agonists. Using the more aggressive LPS protocol, IVF success rates with a GnRH agonist trigger were comparable to those observed when hCG was used for final egg maturation. In 2011 Humaidan et al. reviewed 6 recent RCTs employing a protocol of more aggressive LPS (3 RCTs with aggressive high dose progesterone and estrogen supplementation LPS, 2 RCTs with the addition of low-dose hCG LPS, and one RCT with progesterone and recombinant LH LPS). Importantly, the live birth rate per fresh IVF embryo transfer cycle improved significantly when modified luteal support was used. There were no cases of severe OHSS reported after GnRH agonist triggering, but a 4.6% incidence of severe OHSS was observed in the hCG trigger group for a risk difference of 5% (95% CI -0.07 to 0.02).⁵³ These results support GnRH agonist triggering as an alternative to hCG triggering when a fresh embryo transfer is planned, resulting in a reduction of OHSS and the potential to preserve IVF success rates with adequate LPS. It is not yet clear whether using a GnRH agonist trigger with aggressive LPS results in the same pregnancy rate with fresh embryo transfer as using hCG to trigger final oocyte maturation.

Although the optimal protocol of luteal supplementation has not yet been defined, 2 approaches to luteal phase support in agonist-triggered cycles have been proposed. The first approach is to use aggressive steroid supplementation with progesterone and estrogen, allowing the corpus luteum to degenerate and reduce the risk of OHSS.⁵⁴ The second approach is to attempt rescue of the corpus luteum by administering a low dose of hCG on the day of oocyte retrieval in addition to standard LPS with vaginal progesterone and oral estrogen.^{55,56} The latter approach may need fine tuning because hCG may exacerbate the risk of OHSS and has mostly been examined in a population that was not at high risk for OHSS.⁵² For cycles in which an oocyte donor is stimulated or for fertility preservation cycles in which embryo transfer is not going to occur, a GnRH antagonist pituitary suppression protocol is recommended. This will offer an option for a GnRH agonist trigger to help obviate OHSS risk without affecting pregnancy rates, because a compromised luteal phase is not a concern when embryos are not being transferred into the patient being stimulated. For oocyte donors Lupron 3 mg (0.6 mL) intramuscular 36 hours prior to oocyte retrieval, followed by a repeat dose 10 hours later may be used.

Recommendations

4. Gonadotropin-releasing hormone (GnRH) antagonist stimulation protocols are recommended in patients at high risk for ovarian hyperstimulation syndrome (OHSS). The risk of severe OHSS in patients on GnRH antagonist protocols who have a very robust ovarian stimulation response can be reduced by using a GnRH agonist as a substitute for human chorionic gonadotropin to trigger final oocyte maturation. (I-B)
5. A gonadotropin-releasing hormone (GnRH) antagonist protocol with a GnRH agonist trigger for final oocyte maturation is recommended for donor oocyte and fertility preservation cycles. (III-C)

Prolonged hospitalization with severe OHSS tends to occur more commonly in pregnancy cycles. Cryopreservation of all embryos prevents the possibility of pregnancy in that cycle. The strategy of freezing all embryos in a patient at risk for severe OHSS can prevent prolonged hospitalization, yet still offer hope for a pregnancy with a subsequent transfer of thawed embryos. Avoiding the risk of OHSS needs to be balanced against the possibility of having poor embryo survival, a reduced chance of success after thawing, and a later embryo transfer. However, since vitrification has become available at many treatment centres, the efficiency of cryopreservation programs has increased dramatically, with significantly increased embryo survival rates and higher ongoing pregnancy rates than slow freezing techniques.^{57,58}

A trial comparing cryopreservation of all embryos with fresh embryo transfer alone found a lower incidence of OHSS in the group in which all embryos were cryopreserved than in the fresh embryo transfer group (0/58 vs. 4/67), although this difference did not reach statistical significance.⁵⁹ Garcia-Velasco et al. compared their experience with agonist triggering and oocyte vitrification in patients at high risk of developing OHSS with coasting in 248 patients undergoing IVF who were at risk for OHSS.⁴⁷ Ninety-six patients were triggered with the agonist, with their eggs vitrified and then transferred after thawing and fertilization in a subsequent cycle, and 152 were coasted and then had a fresh embryo transfer.⁴⁷ The clinical pregnancy and implantation rates were significantly higher with transfer of frozen-thawed embryos in a subsequent cycle than with fresh embryo transfer after coasting (50% vs. 29.5%, and 32.1% vs. 19.2%, respectively). There were no cases of OHSS in the cryopreservation and subsequent embryo transfer group, but an 18.7% rate of moderate OHSS in those women who were coasted, with additional cases that were cancelled for being at extremely high risk for OHSS even after coasting.

In patients at high risk for OHSS on a GnRH antagonist protocol, GnRH agonist trigger followed by embryo cryopreservation of all embryos is a good option for preventing OHSS.

Summary Statements

7. Avoiding pregnancy by freezing all embryos will prevent severe prolonged ovarian hyperstimulation syndrome in patients at high risk. (II-2)
8. Pregnancy rates are not affected when using gonadotropin-releasing hormone (GnRH) agonists in GnRH antagonist protocols for final egg maturation when embryos are frozen by vitrification for later transfer. (II-2)

A number of clinical trials have yielded conflicting results on the use of intravenous fluids such as albumin, HES, Haemaccel, and dextran at the time of egg retrieval as a possible way to prevent the severe form of OHSS. It has been speculated that prophylactic intravenous fluid administration may interrupt the development of OHSS by increasing the plasma oncotic pressure, restoring intravascular volume, and deactivating ovarian mediators involved in the pathogenesis of OHSS.⁶⁰ Intravenous administration of fluids such as human albumin, HES, Haemaccel, and dextran infusion immediately post oocyte retrieval or shortly thereafter have also been reported.⁶⁰

In 2011 a Cochrane review of 8 RCTs comparing human albumin and placebo in 1660 patients and HES and placebo in 487 patients at risk for OHSS found a borderline statistically significant decrease in the incidence of severe OHSS with the administration of human albumin (8 RCTs; OR 0.67; 95% CI 0.45 to 0.99).⁶⁰ Although there was also some supportive evidence for the use of HES in preventing OHSS, the safety of HES has not been established and more studies are needed to fully address its use. No RCT compared either dextran or Haemaccel with placebo or no treatment. The cumulative literature does not support the use of intravenous albumin around the time of egg retrieval for the prevention of OHSS.

Recommendation

6. Albumin or other plasma expanders at the time of egg retrieval are not recommended for the prevention of ovarian hyperstimulation syndrome. (I-E)

Elective Single Embryo Transfer

It is well-known that endogenous hCG levels are significantly higher in multiple pregnancies than in singleton pregnancies.⁶¹ If an embryo transfer is being planned in a young patient who is thought to be at significant risk for OHSS based on underlying risk factors, elective single

embryo transfer should be advised. This may decrease the risk of multiple gestations and should in turn decrease the risk of severe OHSS.

Recommendation

7. Elective single embryo transfer is recommended in patients at high risk for ovarian hyperstimulation syndrome. (III-C)

In patients undergoing controlled superovulation with pituitary suppression and oocyte retrieval, luteal phase hormonal supplementation is needed to maximize the chance of pregnancy.⁵³ HCG is effective at providing LPS, however, it plays a vital role in precipitating OHSS and may worsen established OHSS. In a meta-analysis of RCTs, progesterone was established as being equally effective as hCG for LPS and it is associated with a lower risk of OHSS.⁶²

Recommendation

8. Progesterone, rather than human chorionic gonadotropin, should be used for luteal phase support. (I-A)

Culdocentesis

Active outpatient intervention in the early stages of OHSS can minimize associated complications.⁶³ Culdocentesis may alleviate patient discomfort and function to precipitate diuresis in women who are oliguric.⁶⁴ Culdocentesis can be offered in an attempt to prevent disease progression in severe OHSS and eliminate the need for hospital admission.⁶³

Recommendation

9. Outpatient culdocentesis should be considered for the prevention of disease progression in severe ovarian hyperstimulation syndrome. (II-2B)

SUMMARY

Risk-factors and response to ovarian stimulation are limited in their ability to assist in the prediction of OHSS disease occurrence. This becomes evident as some OHSS cases occur in patients not thought to be at significant risk, while the majority of high-risk cases do not result in OHSS.¹ Experience with controlled ovarian stimulation and knowledge of OHSS pathophysiology, risk factors, and clinical presentation remains essential for the prevention of severe OHSS.

In spite of limited understanding of the pathophysiology of OHSS, there is now good evidence that preventive strategies can profoundly reduce the incidence of severe OHSS. Prior to the start of controlled ovarian stimulation,

the addition of metformin in patients with PCOS undergoing IVF should be considered as it may reduce the incidence of OHSS. During the treatment cycle, clinical risk factors should be used in judging the starting doses of gonadotropins. In patients with a very robust response to gonadotropins, coasting should be considered to prevent later OHSS. At the time of hCG trigger, the use of Cabergoline has been shown to reduce the risk for severe OHSS in patients at risk for this complication. There is no strong evidence to support hCG trigger dose as an effective means to decrease the risk of OHSS. Cycle cancellation by withholding hCG has consistently been shown to obviate the risk of OHSS. Avoiding pregnancy by freezing all embryos will prevent severe prolonged OHSS in patients at high risk. Evidence also suggests that a GnRH agonist trigger followed by cryopreservation of all embryos is comparable to cycle cancellation in its efficacy at preventing OHSS with little compromise in success rates in those IVF centres that have a good embryo cryopreservation program. Finally, progesterone should be used for LPS rather than hCG. Continued research is required to gain a better appreciation of the pathophysiology of OHSS, which may advance our ability to predict and prevent this potentially serious illness.

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